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Safety and Efficacy of Purified Factor IX Concentrate and Antifibrinolytic Agents for Dental Extractions in Hemophilia B

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This study evaluated the safety and efficacy of combined treatment with ε-aminocaproic acid or tranexamic acid and monoclonal antibody purified factor IX (MAb factor IX) for prophylaxis against bleeding in eight hemophilia B patients undergoing nine dental extraction procedures. All patients achieved excellent hemostasis without clinical evidence of thrombosis. There were no significant changes in hemoglobin or hematocrit or in markers of hemostatic system activation (prothrombin fragment F_{1+2}, fibrinopeptide A, and fragment $B\beta_{15-42}$) after surgery. Thus, a highly purified factor IX concentrate and antifibrinolytic therapy can be effectively and safely combined in hemophilia B patients undergoing dental extractions. © 1996 Wiley-Liss, Inc.

Key words: monoclonal antibody, thrombosis, factor IX, hemophilia B

INTRODUCTION

The use of antifibrinolytic agents following a single infusion of factor VIII replacement is standard management for dental extractions in hemophilia A [1]. Management of dental surgery in hemophilia B is more problematic because the combination of prothrombin complex concentrates (PCCs) and antifibrinolytics may increase the risk of thrombotic complications [1–3].

The development of highly purified factor IX concentrates with a low potential for abnormal activation of clotting [4,5] has raised the possibility that these products might be used safely and effectively in hemophilia B patients who require dental surgery. The present study was undertaken to evaluate the safety and efficacy of combined treatment with an antifibrinolytic and MAb factor IX in such individuals.

MATERIALS AND METHODS

One hr prior to tooth extraction, patients received approximately 60 U/kg of MAb factor IX (Mononine, Armour Pharmaceutical, Collegeville, PA). Factor IX levels were determined both before and 15–30 min after the infusion. Beginning 4–6 hr after surgery, patients were administered 0.1 g/kg of ε-aminocaproic acid (EACA) (Amicar, Immunex, Seattle, WA), not to exceed 6 g po qid for 10 days. Patients were switched from EACA to tranexamic acid (AMCA) (Cyklokapron, Kabi Pharmacia, Piscataway, NJ) (10 mg/kg tid) if they experienced intolerable side effects.

Two, 10, and 30 days after completion of therapy, the overall efficacy of combined treatment was rated as: excellent (normal hemostasis), good (slight oozing), fair (mild bleeding), poor (moderate bleeding), or none (severe bleeding). Adverse experiences, including any evi-

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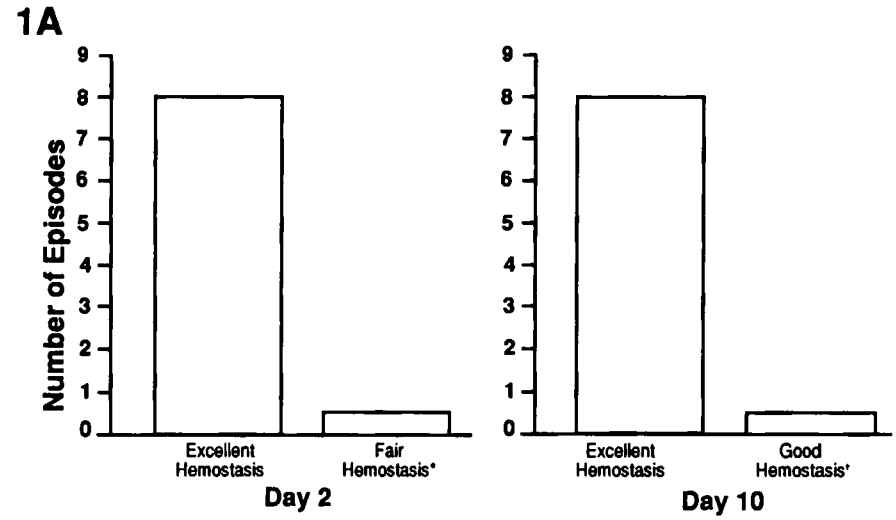

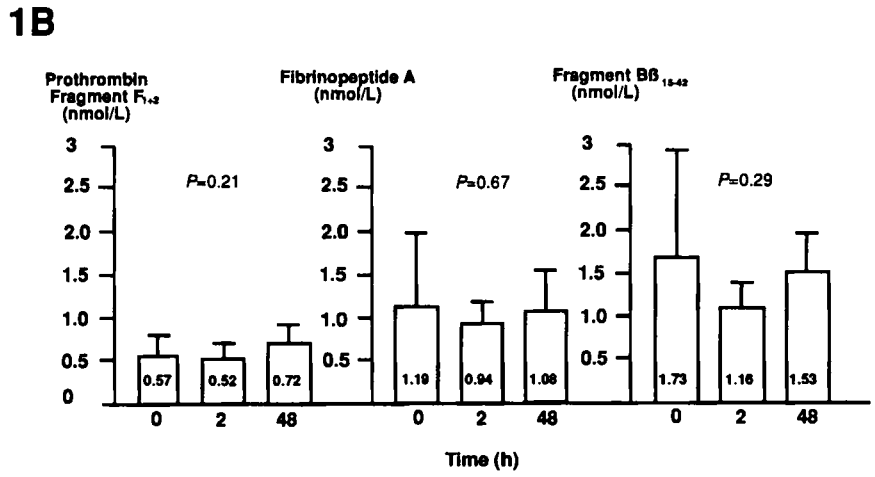

Fig. 1. A: Clinical evaluations of hemostasis 2 and 10 days after dental extractions. B: Average values for prothrombin fragment F_{1+2}, fibrinopeptide A, and fragment $B\beta_{15-42}$ 0, 2, and 48 hr after surgery.

dence of thrombotic complications, were recorded throughout the follow-up period.

Hemoglobin and hematocrit were determined on days 1 and 10 of the follow-up period. Molecular markers of thrombosis (prothrombin fragment F_{1+2}, fibrinopeptide A), and fibrinolysis (fragment $B\beta_{15-42}$) were evaluated just before, and 2 and 48 hr after, dental extraction.

RESULTS

Eight patients entered the trial (one entered twice). The median age was 32 years (range = 21–45 years), the median number of teeth extracted was 4 (range = 1–17 teeth), and the median baseline level of factor IX was 4.5% (range = 2.4–26.0%). All patients received only one dose (averages = 61.5 U/kg and 4,670.5 U) of MAb factor IX. It increased factor IX levels from a pretreatment average of 12.3 ± 10.9% to 81.7 ± 34.8%. All patients were treated with an EACA dose of 24 g/day, but four were switched to AMCA after 1 day. Four patients had hepatitis C, two of whom were human immunodeficiency virus (HIV) positive, with abnormal liver function tests.

All dental extractions were accomplished without complications. No patient required additional doses of MAb factor IX. Two days after surgery, hemostasis was rated as "excellent" for eight episodes and fair in one episode.

Ten days after surgery, hemostasis was rated as "excellent" for eight episodes and good in one episode (Fig. 1A). There were no clinical episodes of thrombotic complications throughout the 30-day follow-up period.

There were no significant differences between hematocrit (43.9 ± 3.6 vs. 43.1 ± 3.0, $P = 0.74$) and hemoglobin (14.9 ± 1.3 vs. 14.6 ± 1.2, $P = 0.65$) measured at or 10 days after surgery.

The average values for prothrombin fragment F_{1+2} at 0, 2, and 48 hr after surgery were 0.57 ± 0.25 nmol/L, 0.52 ± 0.21 nmol/L, and 0.72 ± 0.28 nmol/L ($P = 0.21$). The respective values for fibrinopeptide A were 1.19 ± 0.79 nmol/L, 0.94 ± 0.34 nmol/L, and 1.08 ± 0.51 nmol/L ($P = 0.67$), and those for fragment $B\beta_{15-42}$ were 1.73 ± 1.18 nmol/L, 1.16 ± 0.27 nmol/L, and 1.53 ± 0.46 nmol/L ($P = 0.29$).

Four patients reported adverse events during EACA treatment; three experienced nausea and vomiting, and one experienced nausea and transient elevation in creatine phosphokinase.

DISCUSSION

Clinical results indicated that all patients achieved excellent hemostasis, and there was no laboratory evidence of activation of coagulation factors. These results are consistent with those of previous studies, which indicated that monotherapy with MAb factor IX, as well as with other highly purified factor IX concentrates do not produce significant increases in levels of indicators of coagulation system activation or fibrinolysis [6–10]. They also contrast sharply with findings demonstrating marked elevations in these indices after administration of PCCs [7–9].

Supplementing a single dose of MAb factor IX with antifibrinolytic agents provides a safe and effective treatment in this setting while minimizing the need for replacement factor. Prospective trials can confirm the efficiency of this approach in hemophilia B.

CONCLUSION

This first prospective trial, which included measurements of hemostatic activation, indicates that antifibrinolytic agents and MAb factor IX concentrate provide safe and effective hemostatic coverage in hemophilia B patients undergoing dental extractions.

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NOTE ADDED IN PROOF

Since submission of this manuscript we also extracted two teeth in a 57-year-old patient with mild hemophilia B. Hemostasis was rated as excellent and no adverse reactions were noted after prophylaxis with MAb factor IX and AMCA.

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